# Bristol-Myers Squibb
# Pharmaceutical Research Institute

P.O. Box 4000 Princeton, NJ 08543-4000
609 252-5992 Fax: 609 252-3619





**Laurie Smaldone, M.D.**
Senior Vice President
Worldwide Regulatory Affairs


May 5, 1999

Dockets Management Branch
Food and Drug Administration, HFA-305
5630 Fishers Lane, Room 1061
Rockville, MD 20857

**Re: Docket No. 98D-1168; Proposed Draft Guidance for Industry on "ANDAs: Impurities in Drug Products"; Federal Register [Volume 64, No.2, Tuesday, (January 5, 1999)]**

Dear Sir or Madam:

Bristol-Myers Squibb is a diversified worldwide health and personal care company with principal businesses in pharmaceuticals, consumer medicines, beauty care, nutritionals and medical devices. We are a leading company in the development of innovative therapies for cardiovascular, metabolic, oncology, infectious diseases, and neurological disorders.

The Bristol-Myers Squibb Pharmaceutical Research Institute (PRI) is a global research and development organization that employs more than 4,300 scientists worldwide. PRI scientists are dedicated to discovering and developing best in class, innovative, therapeutic and preventive agents, with a focus on ten therapeutic areas of significant medical need. Currently, the PRI pipeline comprises more than 50 compounds under active development. In 1998, pharmaceutical research and development spending totaled $1.4 billion.

For these reasons, we are very interested in and well qualified to comment on the FDA draft "Guidance for Industry: ANDAs: Impurities in Drug Products".

Summary of BMS Comments on The Proposal

The Agency should be commended for it attempts to standardize and clearly communicate its expectation to the regulated industry. It is only through frank and honest discussions of Agency policy and the scientific basis for that policy, that both the agency and the regulated industry can work as partners to assure a constant supply of quality pharmaceuticals. The efforts of the agency to address the international regulatory community's concerns in a uniform manner, through the incorporation of the ICH guidelines in their policy formation are also appreciated.

98D-1168

C7

In general, the draft proposal clearly addresses agency and regulated industry concerns over harmonizing US FDA requirements with those of the international community. The application of common standards to both new and old drug products is a sound policy basis, as long as information and experience associated with the older products is not discarded. When changes to the control of an older product are necessary, there should be a sufficient transition period to assure that a constant supply of pharmaceuticals to patients is maintained. With these issues in mind, we have the following comments to the draft guidance.

In general, BMS agrees: (1) that the purity standards should be rigorous, but insists that FDA must apply the same purity standards to both generic and innovator drugs; (2) that USP or other compendial standards should provide a minimum for purity standards with no exceptions for products that fail to meet such an established standard (recognizing that in some instances, additional analysis may be appropriate); and (3) that FDA should not approve ANDAs for generic drugs containing degradation products that are not present in the reference listed drug.

As new and improved analytical methods are applied to established drugs, new impurity profiles will be developed. There should be a transition period following the final guidance that allows manufacturers sufficient time to develop and validate the assays/impurity test methods for these "old" drugs, and to set appropriate limits for specific impurities and degradation products. These limits must be based on historical data and established manufacturing capabilities, not on the mere presence of recently identified impurities.

Specific Comments

Analytical methods and limits are developed by the innovator and submitted to the NDA. This information is proprietary as it represents internal technical know-how related to the drug and dosage form in question. Therefore, analytical methods and limits should be held in confidence by the agency when submitted to an IND or NDA and not distributed through FOI or through other means.

We object to the provision in the draft for degradation product levels to exceed the reference drug by a factor of two as scientifically unsound. Stuart Nightingale, FDA's Associate Commissioner for Health Affairs, expressed the FDA's commitment to purity for generic drugs in a 1998 letter to health practitioners regarding therapeutic equivalence for generic drugs: "For both brand-name and generic drugs, FDA works with pharmaceutical companies to assure that all drugs marketed in the US meet specifications for identity, strength, quality, purity and potency. In approving a generic drug product, the FDA requires many rigorous tests and procedures to assure that the generic drug is interchangeable with the brand-name drug under all indications and conditions of use." The implied message of Nightingale's letter is inconsistent with the draft guidance, which would permit degradation production product levels in generic drugs to exceed the levels in the reference listed drug by a factor of two. It is likely that consumer confidence in generic drugs would suffer if they knew that generic manufactures were not held to the same purity standards as the innovators. NDAs have these limits qualified based on human and animal studies, and linked to the stability of the product. The provision to double an impurity limit is not available to the innovator, nor is it allowed by ICH Q3B. All sponsors

(whether for NDAs or ANDAs) should meet the ICH standards, as outlined in Q3B and should not be allowed to double the qualified threshold. The method recommended by the Agency to determine impurity limits is also scientifically unsound. As the Referenced Listed Drug (RLD) product is used to establish at least some, if not all, of the impurity profile, the purchase of the RLD usually precedes the manufacture of the generic product, not the contrary. Also, it is virtually impossible to assure a "fresh batch" of the RLD as the manufacture date is not contained on the product label and most pharmaceutical wholesalers by law use a FIFO distribution system. As the impurity limits are based on recommended storage conditions, it would be scientifically more valid to obtain RLD product at or near its expiration date to determine a valid limit. Use of such product would preclude the need for a two-fold increase in the limits determined on supposedly "fresh" RLD. Finally, the Agency needs to address how they will reconcile different impurity limits between ANDAs established on RLD profiles. If one applicant was able to observe a 2% individual impurity limit in the RLD and a second applicant was able to observe a 1.5% limit, which limit would be used? Shouldn't the limit be the same for both products? And in fact, shouldn't the more rigorous limit be the one followed?

The draft guidance also allows qualification of new or higher level degradation products via Quantitative Structure Activity Relationship studies (QSAR). This provision is not allowed for NDAs nor is it part of ICH Q3B. The approval of an ANDA that has a significantly different impurity profile than the reference listed drug, based merely upon QSAR, is an excellent example of FDA's failure to adhere to its policy of applying the same standards to generic and innovator products. QSAR should not be used in qualifying new or higher levels of degradation products in ANDAs.

The basis for qualification of impurities for new products (i.e. NDAs) is genetic and whole animal toxicology testing according to FDA guidance and ICH Q3B. The proposed ANDA guidance requires only QSAR analysis or genetic toxicology, which is inadequate to assess the toxicology of new degradation products according to current FDA practice and ICH Q3B. Since additional (whole animal or in vivo) toxicology studies cannot be used for generic drug products, an NDA would be required. Therefore, in situations where new degradation products appear, we believe the product is substantially different from the innovator and that an ANDA cannot be used to gain approval.

Starting on line 76, this paragraph indicates that degradation products in stability studies need to be identified only when they exceed established thresholds "at recommended storage conditions". It should be made clear, consistent with line 151, that degradation products observed under accelerated conditions must also be qualified/identified. This is critical. Whereas FDA requires multiple long-term/real-time stability batches and data for NDA approval, but only a single short-term/accelerated stability batch and data for ANDA approval. The alternative would be to require the ANDA sponsor to conduct multiple long-term/real-time stability batching and testing consistent with the NDA sponsor's obligations.

Concerning the section starting on line 157, where the USP or other recognized international monograph establishes a degradation product limit, this limit should be used. Reviewer establishment of alternative limits should be actively discouraged by the Agency. If an alternative limit is recommended, it should only be accepted by the Agency OR the applicant

upon being published in the USP monograph consistent with current Agency MAPPs. This will assure a level playing field for all participants in the drug approval process.

Bristol-Myers Squibb appreciates the opportunity to provide comments to FDA on the draft guidance and respectfully requests that the Agency give consideration to our recommendations.

We would be pleased to provide additional pertinent information as may be requested.

Sincerely,

Laurie F. Smaldone/Joan Kenney

Laurie F. Smaldone, M. D.
Senior Vice President
Worldwide Regulatory Affairs

Bristol-Myers Squibb Company

655 15th Street, N.W. Washington, DC 20005

Dockets Management Branch
Food and Drug Administration, HFA-305
5630 Fishers Lane, Room 1061
Rockville, MD 20857

Return Requested

BMSC-277-10M-73988-10/90

(301) 827-6860

First Class Mail